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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/085,476 | 02/27/2002 | Raffaele De Francesco | IT0002PCA | 5843 |

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| EXAMINER | |
|---|---|
| HUTSON, RICHARD G | |
| **ART UNIT** | **PAPER NUMBER** |
| 1652 | |

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/085,476 | DE FRANCESCO ET AL. | |
| | Examiner | Art Unit | |
| | Richard G. Hutson | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8-12,14,17,18 and 20-23* is/are pending in the application.

4a) Of the above claim(s) *8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,17,18,22 and 23* is/are rejected.

7)☒ Claim(s) *20 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicants amendment of claim 12, the cancellation of claims 13 and 15 and the addition of new claims 20-23, in the paper of 4/28/2005, is acknowledged. Claims 8-12, 14, 17, 18, 20-23 are present and at issue.

Applicants' arguments filed on 4/28/2005, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 8-11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

### *Claim Objections*

Claims 20-23 are objected to because of the following informalities:

Claim 20 (claim 21 dependent on) and 22 ( claim 23 dependent on) recites "...absence of said compound..." and "...ability of said compound...". It is suggested that these recitations be amended to "...absence of said **test** compound..." and "...ability of said **test** compound..."

Appropriate correction is required.

### *Claim Rejections - 35 USC 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12, 14, 17, 18, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al. (Journal of Virology 67(7): 4017-4026, July 1993). The rejection was stated in the previous office action as it applied to previous claims 12, 14, 17 and 18 and repeated below.

Tomei et al. teach that the Hepatitis C virus (HCV) is considered to be the major etiologic agent of post-transfusion non-A, non-B hepatitis and that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa. Tomei et al. also teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome, acting as a component of the replication complex involved in the reaction (page 4024, column 1, paragraph 5). Tomei et al. further teach DNA constructs and transient expression of the HCV genome and characterize the post-translational processing of the HCV transcript, and specifically transcribe and translate NS5B, described by SEQ ID NO: 1. (see page 4020, Figure 1 and also Figure 3A).

One of ordinary skill in the art at the time of the filing of the invention would have been motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA

polymerase, wherein said incubation takes place *in vitro* in order to further characterize the function and role of the protein(s) encoded by the NS5B ORF. The expectation of success comes from the high degree of skill in the art with respect to protein expression, as demonstrated by Tomei et al. in their expression of the HCV cDNA encoding the entire polyprotein using a vaccinia virus T7 expression system. One of ordinary skill at the time of invention would have been motivated to produce the NS5B protein both by the independent transcription and translation of the NS5B as well as by the proteolytic processing of the NS2-NS3-NS4-NS5 polyprotein to determine if the proteolytic processing event affects the activity of the NS5B protein product. One would have been further motivated to vary the RNA templates and primers in the incubation mixture to characterize the specific mechanism of action of any RNA-dependent RNA polymerase activity. The motivation for the addition of ribonucleotide substrates and a RNA template comes from the suggestion by Tomei et al. that the NS5B encodes a RNA-dependent RNA polymerase. The reasonable expectation of success comes from the teaching of Tomei et al. that while the nonstructural region of the HCV genome has not been characterized in detail, it is thought to be processed in a manner similar to that of flaviviruses and pestiviruses and the hydropathy profile of HCV polyprotein is similar to that of the flavivirus polyprotein as well as the suggestion that the NS5B ORF encoded protein is a RNA-dependent RNA polymerase. One of ordinary skill in the art at the time of filing of the application would have been further motivated to incubate together the HCV NS5B protein, ribonucleotide substrates and a RNA template under conditions suitable to produce RNA-dependent RNA polymerase activity, wherein said

incubation takes place *in vitro* in the presence of potential target molecules which may inhibit the action of the NS5B protein as a means of identifying potential therapeutics to be used against the NS5B protein and HCV. The motivation for why one of skill in the art would be interested in the function of the NS5B ORF is because as one of only a few HCV encoded nonstructural proteins the protein(s) encoded by the NS5B ORF is a prime target for the development of therapeutics against HCV. A reasonable expectation of success comes from the high degree of knowledge in the art with respect to protein expression and the identification of inhibitors of said proteins activity, as discussed above.

In response to the previous rejection, applicants have amended claim 12 (claims 14, 17 and 18 dependent on), added new claims 20-23 and traverse the rejection as it applies to the newly amended claims. Claims 22 and 23 are included in the rejection for the same reasons previously stated for claims 12, 14, 17 and 18.

Applicants continue to traverse the rejection on the basis that Tomei et al. fails to demonstrate that NS5B (1) corresponds to an authentically produced HCV protein; (2) is responsible for producing RNA-dependent RNA polymerase activity; and (3) can be successfully purified. Applicants further submit that the prior art fails to provide a reasonable expectation of success in modifying Tomei et al. to produce the claimed assay.

In applicants traversal, applicants characterize the Tomei et al. reference, the various motivations and expectation of success discussed in the previous rejection. In traversing the rejection, applicants suggest that prior to the present application, it was

not known whether HCV NS5B produced in recombinant expression systems such as that employed by Tomei et al. corresponded to a naturally produced product and applicants submit a number of references illustrating these uncertainties, such as differences in molecular weight etc...

Applicants further argue additional considerations such as the apparent failure and difficulty encountered by others and long-felt need.

Applicants' complete argument is acknowledged, however, continues to be found non-persuasive for the reasons previously stated on the record and those below.' With respect to applicants submission that Tomei et al. fails to demonstrate that NS5B (1) corresponds to an authentically produced HCV protein; applicants' point is unclear as to how "whether NS5B corresponds to an authentically produced HCV protein" relates to the currently rejected claims. If applicants are attempting to argue with respect to the expectation of success, as previously stated, Tomei et al. teach that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa and the NS5B region contains a GDD sequence characteristic of RNA-dependent RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome. It would appear absent sufficient evidence to the contrary that the "NS5B corresponds to an authentically produced HCV protein". With respect to applicants submission that Tomei et al. fails to demonstrate that NS5B (2) is responsible for producing RNA-dependent RNA polymerase activity, as previously stated, Tomei et al. teach that the NS5B region contains a GDD sequence characteristic of RNA-dependent

RNA polymerases (RdRp) and they suggest that this protein may act as a viral RNA replicase during HCV-specific RNA synthesis and also function in the replication of the viral genome. Applicants are reminded that the current rejection is based on obviousness, not anticipation. With respect to applicants submission that Tomei et al. fails to demonstrate that NS5B (3) can be successfully purified, Tomei et al. teach that the NS5 region of the HCV polyprotein is cleaved into two smaller products of 47 and 65 kDa, and Tomei et al. successfully purify each of these smaller products. While it is acknowledged that purification can be to various degrees, the purification of the NS5 gene products as well as other teachings of Tomei et al. are sufficient to make the rejected claims obvious.

Applicants further submit that the prior art fails to provide a reasonable expectation of success in modifying Tomei et al. to produce the claimed assay

Finally with respect to applicants comments regarding the apparent failure and difficulty encountered by others as well as a long-felt need, applicants comments are acknowledged, however, not found persuasive. Applicants are reminded that this is a rejection based on the obviousness of the claimed methods and that applicants should argue such that applicants arguments are clearly directed to the rejection of record, as it applies to the claimed methods.

Thus claims 12, 14, 17 and 18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tomei et al.

***Terminal Disclaimer***

The terminal disclaimer filed on 4/28/2005 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,383,768 has been reviewed and is accepted. The terminal disclaimer has been recorded.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

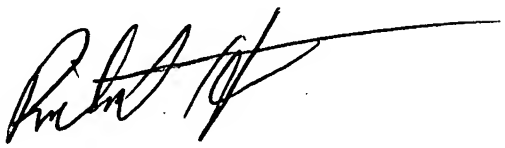
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax

phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
7/21/2005